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| EXAMINER |
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ZEMAN, ROBERT A

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1645

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08/18/2009

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

08/844,336

Applicant(s)

CONTAG ET AL.

Examiner

ROBERT A. ZEMAN

Art Unit

1645

Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 23 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 3-9, 21, 22 and 25-27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-9, 21, 22 and 25-27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/C)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____
- Paper No(s)/Mail Date _____

DETAILED ACTION

The Appeal Brief filed on 9-17-2007 is acknowledged. Upon careful review of the record the finality of the last Office action is withdrawn. Applicant's arguments, as set forth in said Appeal brief, will be addressed below.

Claims 1, 3-9, 21-22 and 25-27 are pending and currently under examination.

Claim Rejections Withdrawn

The rejection of claim 21 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the use of the phrase "derived from PhoQ" is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1, 3-9, 22 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Menzel et al. (U.S. Patent 5,521,066) in view of Georgiou et al. (U.S. Patent 5,348,867 – IDS filed on 1-22-99) is maintained for reasons of record.

Applicant argues:

1. The Examiner is ignoring the plain meaning of the terms used in the construction of the instant claims. The terms “ligand-binding domain” and “transducer” would be recognized by the skilled artisan as excluding Menzel’s system.
2. The term “ligand –binding domain” and “dimerization domain” are used in the art to describe different binding domains (as set forth in Menzel).
3. The term “transducer” is clearly understood by the skilled artisan to be separate from the intracellular domain and the responsive element.
4. The specification clearly defines a ligand binding domain as not requiring ligand-mediated dimerization (page 15, lines 1-7 of specification).
5. The specification clearly defines a transducer as a separate molecule (see page 16, lines 11-15 of the specification).
6. Menzel’s system is based on dimerization, the ligand domain is optional and expression of the reporter gene is linked to dimer formation not ligand binding.
7. There is no transducer in Menzel’s system.

8. Menzel does not teach or suggest a biodetector in which the extracellular domain is an antibody which binds to a ligand and wherein said binding triggers the expression of a reporter gene.

9. There is no motive to substitute Georgiou's scFv antibodies for Menzel's dimerization domain or ligand binding domain, because such substitutions would destroy the intended function of Menzel's system.

Applicant's arguments have been fully considered and deemed non-persuasive.

The instant claims are drawn to a biodetector comprising a transmembrane fusion protein comprising an extracellular ligand-specific moiety comprising an antibody and an intracellular enzymatic signal-transforming domain (i.e. signal-converting element); a transducer and a responsive element (transcription activation element) optionally coupled to a reporter gene (luciferase) via said responsive element. Said biodetector may further comprise a bacterial cell.

With regard to Points 1 and 2, the dimerization domain is a type of ligand-binding domain. As clearly illustrated by the portion of Menzel cited by Applicant, the dimerization domain forms a dimer "... as a result of ligand binding and the like". Consequently, the dimerization domain of Menzel is clearly encompassed by the "ligand-binding domain" of the instant claims.

With regard to Points 1 and 3, the definition of the term "transducer" would not be as narrowly construed as indicated by Applicant. The term encompasses any molecule that conveys a signal from the exterior of the cell to the interior of the cell. As Menzel discloses the cytoplasmic domain of the wildtype or toxR fusion protein induces binding (via a conformational change) to the promoter region (i.e. the transcription activation element) of the reporter gene

(resulting in the expression of the reporter gene) in response to ligand binding to the ligand-binding domain of said fusion protein, the disclosure of Menzel meets the requirements of the instant claims with regard to the transducer.

With regard to Point 4, the cited portion of the specification consists of a non-limiting list of the substances that can be identified using the instant invention. In no way does the cited portion of the specification preclude ligand-mediated dimerization. Moreover, the specification clearly states that the ligand binding domain can be an antibody or derivative thereof (see page 15, lines 9-14)

With regard to Point 5, contrary to Applicant's assertion, the cited portion of the specification (which is actually page 16, lines 14-19 not page 16, lines 11-15) does not define a transducer as a separate molecule. Moreover, the specification clearly states that the transducer can function directly or indirectly on a promoter (see page 16, lines 20-22).

With regard to Points 6, 7 and 9, Menzel discloses that "a variety of ligand-binding domains" could be used (see column 2, lines 15-16). Moreover, contrary Applicant's assertion, the use of antibodies would not render Menzel's system inoperative. Menzel discloses that the "dimerization domain" (i.e. ligand binding domain) can be anything capable of forming a dimer (see column 4, lines 32-36). Since certain antibody classes (e.g. IgA) can form dimers they meet the requirements set forth by Menzel and the instant claims.

With regard to Point 8, the instant claims merely require a component that changes from an inactive to an active form in response to ligand binding and that that "change" activates a responsive element resulting in a detectable signal. As Menzel discloses the cytoplasmic domain of the wildtype or toxR fusion protein induces binding (via a conformational change) to the

promoter region (i.e. the transcription activation element) of the reporter gene (resulting in the expression of the reporter gene) in response to ligand binding to the ligand-binding domain of said fusion protein, the disclosure of Menzel meets the requirements of the instant claims with regard to the transducer.

As outlined previously, Menzel et al. disclose host cells a transmembrane fusion protein comprising a ligand binding domain, a cytoplasmic toxR DNA binding region, a hydrophobic ToxR transmembrane region and a reporter gene operatively linked to the ctx operon (see column 1, line 65 to column 2, line 6). Menzel et al. further disclose that when a ligand binds to the ligand binding domain, the cytoplasmic domain of the fusion protein to undergo a conformational change which induces binding to the promoter region of the reporter gene (see column 2, lines 35-44). Finally, Menzel et al. disclose that their fusion protein can be used to generate signal using a variety of ligand-binding domains (see column 2, lines 15-16) and that any reporter gene known in the art can be used with the disclosed fusion protein (see column 4, lines 38-42) and that the disclosed fusion proteins can be expressed in bacterial hosts (see column 7, lines 7-8).

Menzel et al. differs from the claimed invention in that they do not explicitly disclose the use of the antibodies or derivatives thereof or the specific use of luciferase as the reporter.

Georgiou et al. disclose methods for the recombinant expression of heterologous proteins on the surface of bacteria (see abstract) including the expression of scFv (see column 6, lines 25-26).

Since Menzel et al. disclose that a variety of ligand binding domains can be used in their transmembrane fusion protein, it would have been obvious to one of skill in the art to use the

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heterologous scFv disclosed by Georgiou et al. in order to take advantage of the increase in specificity, diversity and ease of production associated with the resulting fusion protein (biodetector).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 3-9, 21-22 and 25-27 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant argues:

1. It was well known at the time of filing that antibodies expressed as fusion proteins would bind to their selected ligand.
2. Signal transforming domains were also well known in the art at the time of filing.
3. The specification does not need to re-describe what is well known.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1-3, while the components of the instant invention may have been known in the art, the compatibility of said components was not. The instant claims encompass

biodetectors comprising limitless combinations of transmembrane fusion proteins (comprising an extracellular antibody domain and an intracellular enzymatic signal domain), transducers and reporter genes/operons. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The instant claims are drawn to a biodetector comprising a transmembrane fusion protein comprising an extracellular ligand-specific moiety comprising an antibody and an intracellular enzymatic signal-transforming domain (i.e. signal-converting element); a transducer and a responsive element (transcription activation element) optionally coupled to a reporter gene (luciferase) via said responsive element. Said biodetector may further comprise a bacterial cell.

The specification discloses a biodetector comprising a fusion protein consisting of an antibody heavy chain and an active domain of PhoQ, PhoP (signal transducer) and the *lux* operon coupled to the Pho promoter. This biodetector meets the written description provision of 35 USC 112, first paragraph. However, the aforementioned claims are directed to encompass biodetectors comprising limitless combinations of transmembrane fusion proteins (comprising an extracellular antibody domain and an intracellular enzymatic signal domain), transducers and reporter genes/operons. None of these biodetectors meet the written description provision of 35 USC 112, first paragraph. The specification provides insufficient written description to support the genus encompassed by the claim. The transmembrane fusion protein of the claimed biodetector must be able to activate a given transducer via its intracellular enzymatic signal transforming domain upon the binding of the "ligand" to the extracellular antibody. The transducers must be able to trigger either directly or indirectly, the activation of a

transcription activating element (promoter) to effect the activation of the responsive element (reporter gene or operon). The Specification discloses that said transducer may be any molecule that can recognize and respond to a change in conformation, electrical charge, addition or subtraction of any chemical subgroup and is capable of triggering a detectable response (see page 16 of the specification). With the exception of the antibody/PhoQ based biodetector which utilizes PhoP as its transducer and the Pho promoter coupled to the *lux* operon as its responsive element, the specification is silent with regard to what specific combinations of transmembrane proteins, transducers and responsive elements would result in a functional biodetector.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

With the exception of the aforementioned antibody/PhoQ based biodetector, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

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...To fulfill the written description requirement, a patent specification must describe an invention and does so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5 of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5.

Therefore, only aforementioned antibody/PhoQ based bioreactor, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph. The species specifically disclosed is not representative of the genus because the genus is highly variant. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ROBERT A. ZEMAN whose telephone number is (571)272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on (571) 272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

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/Robert A. Zeman/
Primary Examiner, Art Unit 1645
August 17, 2009